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Manganese ions acts as a messenger to regulate serum lipid levels

Cardiovascular disease is the leading cause of mortality for contemporary society [1]. Lipid homeostasis imbalance has been identified as the underlying cause of cardiovascular and related metabolic diseases, leading to the unnoticed development of fatal risks such as atherosclerosis [2].Therefore, regulating lipid metabolism is crucial in preventing and managing cardiovascular diseases, which has led to the development of potent lipid-lowering medications, such as statins and PCSK9 inhibitors. Nevertheless, these interventions are inadequate for meeting the demands of medical treatment, particularly for reversing or eliminating existing atherosclerotic plaques [3].

A substantial quantity of lipids circulates in the form of lipoprotein particles, characterized by the presence of apolipoprotein B (APOB). These lipoproteins, which encompass very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and chylomicrons (CM), accumulate disproportionately in the bloodstream, constituting a significant pathogenic factor for cardiovascular diseases. The process of lipoprotein entry and exit from the bloodstream is tightly regulated. The LDLR was discovered to mediate the entry of LDL from the bloodstream into cells, facilitating the clearance of lipids [4]. However, how the general transport machinery in cells, such as the Coat protein complex II (COPII complex), supports and regulates the transport of specialized and abundant lipoproteins efficiently, remains unknown [5].

COPII gates entry into the secretory pathway at the ER surface [6]. COPII assembly and cargo packaging are initiated upon activation of the small GTPase SAR1, which recruits the inner-coat subcomplex SEC23–SEC24 (SEC23/24), followed by the SEC31–SEC13 (SEC31/13) outer-coat subcomplex [6–8]. In a recent study published in *Nature Cell Biology*, Wang et al. reported that the COPII complex achieves efficient regulation of lipoprotein secretion through unconventional "self--limiting" phase separation, with manganese ions (Mn^{2+}) identified as messenger molecules tuning the balance between COPII protein condensation and dynamics [9]. The authors found that COPII components drive the formation of COPII protein condensates through liquid-liquid phase separation, selectively mediating efficient secretion of lipoproteins under physiological conditions. Remarkably, the authors serendipitously identified that the COPII-mediated "self-limiting" phase separation, which regulates the process of lipoprotein secretion, can be co-opted by adenovirus, a pathogen that frequently co-infects both humans and mice. Through the establishment of *in vitro* recombinant systems and biochemical separation methods, the authors further determined that Mn^{2+}, acting as a messenger, directly binds to the inner coat proteins SEC23/SEC24, dose-dependently promotes the phase separation of COPII and tunes the balance between condensation and dynamics, resulting in a bell-shaped regulation of lipoprotein secretion without affecting the secretion of normal proteins. Additionally, the authors manipulated the "manganese signal" by controlling the dietary intake of manganese in mice. This strategic approach aimed to specifically target liver COPII under physiological and pathological conditions, achieving precise regulation of lipid secretion.

The high accumulation of manganese ions in the liver after intake led the authors to speculate that a therapeutic approach based on the messenger function of manganese could potentially reverse atherosclerotic plaques in clinical settings. To test this hypothesis, the authors used Mn^{2+} to quantitatively activate the manganese signal through dietary

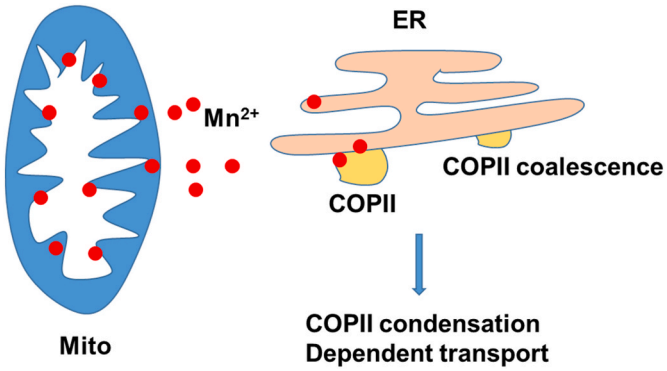

Fig. 1. The mitochondria manganese stores in regulating the condensation-dependent transport of the COPII complex.

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intake in a pathological mouse model of atherosclerosis induced by high blood lipids. Surprisingly, this approach effectively reversed and even eliminated atherosclerotic plaques that had already formed [10].

The authors have identified the COPII complex, a classical mechanism for cell transport, as a quantitative regulator of blood lipid transport through phase separation. Moreover, they have unveiled manganese ion as a messenger that can target COPII phase separation *in vitro*, at the cellular and systemic levels. This precise targeting facilitates the accurate control of lipid levels. Furthermore, this mechanistic understanding holds rare potential for applications in the prevention and treatment of major diseases (see Fig. 1). Notably, the study has successfully demonstrated the reversal of fatal cardiovascular diseases in animal models.

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CRediT authorship contribution statement

Honglin Sun: Conceptualization, Writing – original draft, Writing – review & editing. **Suzhen Chen:** Conceptualization, Writing – original draft, Writing – review & editing. **Junli Liu:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

No conflict of interest to disclose.

References

[1] Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell 2015;161(1):161–72.
[2] Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. Circ Res 2014;114(12):1852–66.
[3] Brandts J, Ray KK. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. Nat Rev Cardiol 2023;20(9):600–16.
[4] Fisher EA, Ginsberg HN. Complexity in the secretory pathway: the assembly and secretion of apolipoprotein B-containing lipoproteins. J Biol Chem 2002;277(20):17377–80.
[5] Wang X, Chen XW. Cargo receptor-mediated ER export in lipoprotein secretion and lipid homeostasis. Cold Spring Harbor Perspect Biol 2023;15(6).
[6] Fath S, Mancias JD, Bi X, et al. Structure and organization of coat proteins in the COPII cage. Cell 2007;129(7):1325–36.
[7] Zanetti G, Pahuja KB, Studer S, et al. COPII and the regulation of protein sorting in mammals. Nat Cell Biol 2011;14(1):20–8.
[8] Bi X, Corpina RA, Goldberg J. Structure of the Sec23/24-Sar1 pre-budding complex of the COPII vesicle coat. Nature 2002;419(6904):271–7.
[9] Wang X, Huang R, Wang Y, et al. Manganese regulation of COPII condensation controls circulating lipid homeostasis. Nat Cell Biol 2023;25(11):1650–63.
[10] Wang Y, Feng X, Zhou W, et al. Manganese therapy for dyslipidemia and plaque reversal in murine models. Life Metabolism 2023. https://doi.org/10.1093/lifemeta/load040.

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